



## ViziLite Plus and OralCDx

### Oral cancer detection aids: to use or not to use

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#### Introduction

Oral cancer, most commonly presenting as a form of squamous cell carcinoma, continues to be a worrisome disease in the United States, with oral cancer mortality rates not significantly improved in the last 40 years. More than 30,000 people will receive a diagnosis of oral cancer this year and only 58% of those will survive 5 years.<sup>1</sup> The overall 5-year survival rate of oral cancer is worse than that of cancer of the breast, colon, kidney, and uterus.<sup>1</sup> Interestingly, 27% of oral cancer victims do not use alcohol or tobacco products and have no other lifestyle risk factors.<sup>1</sup>

Detection of oral cancer in the earliest stages significantly improves patient survival and quality of life by limiting extensive or disfiguring surgery and the possibility of radiation treatment. The 5-year survival rate for patients with localized disease approaches 80%.<sup>2</sup> For patients with distant metastases, the 5-year survival rate drops to 19%.<sup>2</sup> Despite the efforts to improve oral cancer screening, approximately 50% of patients with oral cancer have evidence of regional spread to lymph nodes or local and distant metastases at time of diagnosis.<sup>2</sup> Therefore, early detection of oral cancer is imperative to provide the best chance of survivability and maintaining the best quality of life.

Oral cancer detection aids that claim to help improve the chances of diagnosing oral cancer at the earliest stage possible have recently been marketed to dental professionals. ViziLite Plus with TBlue<sup>630TM</sup> (Zila Pharmaceuticals, Inc.) is an oral lesion identification and marking system that is used as an adjunct to the conventional head and neck examination. OralCDx (Oral Scan Laboratories, Inc.) is a computer-assisted method of analyzing a brush biopsy of suspected precancerous and cancerous lesions in the oral cavity. This clinical update explores the published studies surrounding these two detection systems in an effort to help the clinician decide if these products do in fact improve the ability to detect oral cancer at its earliest stage.

#### ViziLite Plus with TBlue<sup>630TM</sup>

ViziLite Plus with TBlue<sup>630TM</sup> is an identification and marking system designed to help the clinician detect and highlight lesions in the oral cavity that may need biopsy.<sup>3</sup> The system consists of a 1% acetic acid prerinse that the patient swishes for 30-60 seconds and expectorates. The acetic acid wash helps remove surface debris and causes epithelial cells to dehydrate, increasing the prominence of their nuclei. Abnormal epithelium appears a deeper white color. The ViziLite is a small, flexible, disposable light stick that is activated upon breaking an inner vial (chemiluminescence). The light stick is used to illuminate the intraoral mucosal surfaces and tongue to look for lesions that might not otherwise be apparent under traditional lighting conditions. Abnormal squamous epithelium tissue will appear acetowhite from the acetic acid rinse when viewed under ViziLite's diffuse low-energy wavelength light. Normal epithelium will absorb the light and appear dark. The TBlue<sup>630TM</sup> is a toluidine blue-based metachromatic dye which is used to further evaluate and monitor changes in ViziLite-identified lesions. Toluidine blue is a mitochondrial stain that binds to the altered mitochondrial DNA in premalignant and malignant epithelial lesions. The TBlue<sup>630TM</sup> provides deep blue staining that allows ViziLite-identified lesions to be seen clearly

under normal light for biopsy or intraoral photographs for documentation and referral.<sup>3</sup> Therefore, the acetic acid removes debris and dehydrates the epithelial nuclei while the toluidine blue stains the abnormal mitochondrial DNA.

#### Studies on ViziLite Plus

PubMed shows that there have been 5 published studies between 2005 and 2007 chronicling the results of ViziLite Plus. In the first study,<sup>4</sup> 100 patients were screened for oral lesions using unaided visual techniques and traditional lighting. This technique revealed 57 clinically diagnosable lesions (e.g. linea alba, leukoedema) and 29 clinically undiagnosable lesions (leukoplakia). After the 1% acetic acid rinse only, 6 additional diagnosable lesions (linea alba) and 3 additional undiagnosable lesions (leukoplakia) were found. No additional lesions were detected after using the chemiluminescent light. Of the 32 clinically undiagnosable lesions, all lesions were biopsied and 2 were found to have epithelial atypia. Oh<sup>4</sup> concluded that although the 1% acetic acid rinse accentuated some lesions, the overall detection rate using chemiluminescence was not significantly improved. Also, the chemiluminescent light produced reflections that made visualization more difficult and thus was not beneficial. Ram<sup>5</sup> compared ViziLite with tolonium chloride rinse. Thirty-one previously identified clinical lesions (14 squamous cell carcinoma, 10 epithelial dysplasia, 5 lichen planus, and 2 benign hyperkeratosis) and 5 cases of normal mucosa were tested using ViziLite and tolonium chloride respectively. The ViziLite was able to detect 100% of the previously diagnosed lesions and the tolonium chloride identified 70% of the lesions. Ram suggested that chemiluminescence is a more reliable diagnostic tool than tolonium chloride in the detection of oral lesions. A third multicenter study<sup>6</sup> reported the effect of ViziLite upon visualization of mucosal lesions whereby the chemiluminescent light did not appear to improve visualization of red lesions, but white lesions and lesions that were both red and white showed enhanced brightness and sharpness.<sup>6</sup> A study by Kerr et al.<sup>7</sup> concluded oral lesions illuminated by chemiluminescent lighting appeared brighter, sharper, and smaller compared to incandescent illumination, especially on leukoplakic lesions. The fifth study, by Farah and McCullough,<sup>8</sup> concluded that examination of the oral tissues with ViziLite illumination did not change the provisional diagnosis, nor did it alter the biopsy site of intraoral lesions. ViziLite illumination did not discriminate between keratotic, inflammatory, malignant or potentially malignant oral mucosal white lesions. Therefore, expert clinical judgment and scalpel biopsy are still essential for proper patient care. In summary, the studies report that although ViziLite Plus may enhance the visualization of clinically evident intraoral lesions, it did not detect lesions that were not readily recognizable with a thorough clinical exam utilizing traditional lighting.

#### OralCDx Brush Biopsy

OralCDx is a biopsy technique which uses a circular brush to collect epithelial cells from detected intraoral lesions without the need for anesthesia. The brush is rubbed against the lesion in a circular motion until an adequate number of cells is collected on the brush. Clinically, this means the post-biopsy area should have microbleeding or "pinpoint" hemorrhage. The cells from the brush are transferred to a glass slide, attached to the slide by a fixative, and sent to OralCDx for computer-assisted microevaluation. The results provided to the clinician are in 4 categories: "Negative": no epithelial abnormality; "atypical": abnormal epithelium of

uncertain diagnostic significance; “positive”: definitive evidence of cellular dysplasia; “inadequate”: incomplete transepithelial cells for evaluation.<sup>3</sup> OralCDx has the American Dental Association (ADA) Seal of Acceptance. The ADA’s Council on Scientific Affairs acceptance is “based on its finding that the product is an effective adjunct to the oral cavity examination in the early detection of precancerous and cancerous oral lesions, when used as directed. All Oral CDx ‘atypical’ and ‘positive’ results must be confirmed by incisional biopsy and histology to completely characterize the lesion. Persistent lesions even with negative results must receive adequate follow-up evaluations, when used as directed.”<sup>9</sup>

## Studies on OralCDx

From 2000 to present, a significant number of studies and letters to the editor have been published on the controversial OralCDx brush biopsy technique. Some authors believe it is a useful screening tool for potential cancerous and precancerous lesions while others feel nothing is a substitute for a thorough clinical exam and scalpel biopsy. The original published study<sup>2</sup> of 945 patients claimed OralCDx to have a 100% sensitivity and specificity rate for “positive” results and a specificity rate of 92% for “atypical” results. The study concluded OralCDx can aid in confirming the nature of apparently benign oral lesions and, more significantly, reveal those that are precancerous and cancerous when they are not clinically suspected of being so. In another study, Poate<sup>10</sup> reported the sensitivity of detection of oral epithelial dysplasia or squamous cell carcinoma of the oral brush biopsy system was 71%, while the specificity was 32%. The positive predictive value of an abnormal brush biopsy result (“positive” or “atypical”) was 44%, while the negative predictive value was 60%. It was concluded that not all potentially malignant disease is detected with this non-invasive investigative procedure. In a third study by Svirsky, et al.,<sup>11</sup> OralCDx biopsy results were compared with scalpel biopsy and histology to determine the positive predictive value of an abnormal brush biopsy finding. Of 243 patients with abnormal brush biopsies, 93 proved positive for dysplasia (79) or carcinoma (14), and 150 were negative for either dysplasia or carcinoma. Therefore, the positive predictive value of an abnormal brush biopsy was 38% (93/243). Svirsky et al.<sup>11</sup> claimed by using the oral brush biopsy, dentists can inform their patients that abnormal findings have a strong positive predictive value for dysplasia or carcinoma and therefore require follow-up confirmation by scalpel biopsy. Svirsky does go on to say it is imperative oral lesions with negative brush biopsy results should be routinely monitored and excised if they persist, especially in high risk areas such as lateral border of the tongue or floor of mouth. Potter<sup>12</sup> examined 4 cases of OralCDx biopsy negative squamous cell carcinomas identified from 115 total cases of malignancy (3.5%). The average time from brush biopsy to tissue diagnosis was 117.25 days (range, 5 to 292 days). The conclusion was that some false negative reports are possible with the oral brush biopsy technique and that persistent lesions should undergo tissue biopsy for definitive diagnosis.

## Conclusions

The published studies involving ViziLite Plus all have similar conclusions in that the chemiluminescence system can make intraoral lesions, especially leukoplakias, appear sharper and brighter. Even so, none of the studies showed ViziLite Plus able to detect intraoral lesions that a thorough clinical examination with traditional lighting could not detect.

The published studies on OralCDx have varied conclusions as to the clinical usefulness of oral brush biopsies. An interesting trend has general dentists seemingly more supportive of the system while the oral pathology, oral medicine, and oral surgery communities are less enthusiastic (with one notable exception<sup>2</sup>). The OralCDx system can

detect abnormal cells but can not give a definitive diagnosis. Only 4 results are reported after computer analysis: “positive,” “atypical,” “negative,” and “inadequate.” Any “positive” or “atypical” result must be scalpel biopsied and submitted for histologic examination. In this instance, the patients may not understand why they need another biopsy. Also, there is the question of cost reimbursement in private practice for the second biopsy procedure. None of the studies were able to conclude that the OralCDx brush biopsy offers an improvement over a proper clinical oral cancer exam with prudent follow-up of suspicious lesions. All the studies emphasize dentists must rely on their clinical judgment in assessing patients regardless of the results of a negative brush biopsy. The ADA considers the OralCDx an adjunct oral cancer screening system, not a replacement for the traditional oral cancer exam.<sup>9</sup>

## References

1. American Cancer Society. Cancer Facts and Figures 2007. Atlanta: American Cancer Society; 2007.
2. Sciubba JJ. Improving detection of precancerous and cancerous oral lesions. Computer-assisted analysis of the oral brush biopsy. U.S. Collaborative OralCDx Study Group. J Am Dent Assoc. 1999 Oct;130(10):1445-57.
3. Kalmar JR. Advances in the detection and diagnosis of oral precancerous and cancerous lesions. Oral Maxillofac Surg Clin N Am. 2006;18:465-482.
4. Oh ES, Laskin DM. Efficacy of the ViziLite System in the identification of oral lesions. J Oral Maxillofac Surg. 2007 Mar;65(3):424-6.
5. Ram S, Siar CH. Chemiluminescence as a diagnostic aid in the detection of oral cancer and potentially malignant epithelial lesions. Int J Oral Maxillofac Surg. 2005 Jul;34(5):521-7.
6. Epstein JB, Gorsky M, Lonky S, Silverman S Jr, Epstein JD, Bride M. The efficacy of oral lumenoscopy (ViziLite) in visualizing oral mucosal lesions. Spec Care Dentist. 2006 Jul-Aug;26(4):171-4.
7. Kerr AR, Sirois DA, Epstein JB. Clinical evaluation of chemiluminescent lighting: an adjunct for oral mucosal examinations. J Clin Dent. 2006;17(3):59-63.
8. Farah CS, McCullough MJ. A pilot case control study on the efficacy of acetic acid wash and chemiluminescent illumination (ViziLite™) in the visualisation of oral mucosal white lesions. Oral Oncol. 2006 Dec 13; [Epub ahead of print]
9. American Dental Association Council on Scientific Affairs. www.ada.org/ada/seal/ Accessed on 22 March 2007
10. Poate TW, Buchanan JA, Hodgson TA, Speight PM, Barrett AW, Moles DR, Scully C, Porter SR. An audit of the efficacy of the oral brush biopsy technique in a specialist oral medicine unit. Oral Oncol. 2004 Sep; 40(8):829-34.
11. Svirsky JA, Burns JC, Carpenter WM, Cohen DM, Bhattacharyya I, Fantasia JE, Lederman DA, Lynch DP, Sciubba JJ, Zunt SL. Comparison of computer-assisted brush biopsy results with follow up scapel biopsy and histology. Gen Dent. 2002 Nov-Dec;50(6):500-3.
12. Potter TJ, Summerlin DJ, Campbell JH. Oral malignancies associated with negative transepithelial brush biopsy. J Oral Maxillofac Surg. 2003 Jun;61(6):674-7.

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